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FINAL SUMMARY REPORT

The Interaction of Pseudomonas Toxins with Epithelial Cell Membranes; A Primary Stage in the Pathogenesis Sequence of Cellular Intoxication

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FINAL PROGRESS REPORT (1980-81 period)

During the 1980-81 Contract Period the following research information has been discovered:

In pursuing the specific aims of this research contract during the 1980-81 period, we have discovered the following:

1) The degree of purity of a given Pseudomonas toxin A preparation is not necessarily related to the potency of the effect of that toxin on the isolated turtle bladder—even when the same toxin A preparation has proven to be a more potent pathogenetic agent in mammalian host cell systems.

2) There are parallelisms between the inhibitory effects of toxin A and those of chlorpromazine (an adenylate cyclase inhibitor) on Na transport as well as anion transport. These parallelisms are not yet sufficient evidence from which one can infer that toxin A-induced changes in the apical membrane are due to interactions of the inherent ADPRase-containing moiety of this toxin with any of the transport-related, enzymatic components in the apical membrane. This ADPRase is known to catalyze the ribosylation of elongation factor 2 in mammalian host cell systems.

   On the other hand, the inherent ADPRase of another toxin, cholera toxin, has been shown to catalyze the ribosylation and thereby to increase the activity of a membrane-bound adenylate cyclase in avian erythrocytes. In this connection, we have found parallelisms between the stimulating effects of another ADPRase-containing toxin (Cholera toxin) and those of:

   norepinephrine (and other catecholamines which are adenylate cyclase activators);

   cyclic AMP derivatives (protein kinase activators); and

   theophylline (a phosphodiesterase inhibitor).

3) The preparation from turtle bladder cells of isolated, uniformly oriented apical membrane vesicles (right side out or inside out) with the ion transport functions still intact could provide a susceptible sub-cellular host system in which any toxin-induced changes in ion transport rates or in maintained transmembrane gradients of ion concentration could be direct and exclusive consequences of primary plasma membrane alterations. In approaching this aim, we have shown that a suspension of mixed membrane vesicle (apical and basal) actively acidify the external medium; and that it is technically feasible to prepare isolated apical membrane vesicles.

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Abstract and Publication

Brodsky, W.A., G.C. Sadoff, J.H. Durham, G. Ehrenspeck, M. Schachner & B.H. Iglewski
Toxin - induced changes in the luminal membrane of an ion transporting epithelium.
Fed. Proc., 38:1241, 1979

Brodsky, W.A., G.C. Sadoff, J.H. Durham, G. Ehrenspeck, M. Schachner & B.H. Iglewski
Effects of Pseudomnas toxin A, Diphteria toxin and Cholera toxin on the electrical parameters of the turtle bladder.
Proc. Nat'l. Acad. Sci., 76:3562-3566, 1979.

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